We claim:

1. A method of treating diabetes comprising administering a compound that reduces skeletal muscle ketone levels to a diabetic subject in a therapeutically effective amount to reduce skeletal muscle ketone levels.

2. The method of Claim 1, wherein the subject has type 2 diabetes.

3. The method of Claim 1, wherein the compound enhances ketolytic activity in skeletal muscle.

4. The method of Claim 3, wherein the compound enhances the activity of a ketolytic enzyme in skeletal muscle.

5. The method of Claim 1, wherein the compound reduces ketogenic activity in skeletal muscle.

6. The method of Claim 5, wherein the compound reduces the activity of a ketogenic enzyme in skeletal muscle.

7. The method of Claim 1, wherein the compound enhances hepatic fatty acid oxidation.

8. The method of Claim 7, wherein the compound enhances the activity of a hepatic fatty acid oxidizing enzyme.

9. The method of Claim 1, wherein the compound is a succinate ester or a succinate precursor.

10. The method of any of Claims 1-8, wherein the compound is a polypeptide.

11. The method of Claim 9, wherein the compound is an antibody.

12. The method of any of Claims 1-8, wherein the compound is a nucleic acid molecule.

13. The method of any of Claims 1-12, wherein the subject is a human subject.

14. The method of any of Claims 1-13, wherein β-hydroxybutyrate levels are reduced.

15. A delivery vector comprising a heterologous nucleic acid that encodes a ketolytic enzyme, wherein the heterologous nucleic acid is operably linked to a control element that directs the expression of the nucleic acid in skeletal muscle cells.

16. The delivery vector of Claim 15, wherein the ketolytic enzyme is selected from the group consisting of acetoacetate:succinyl CoA:3oxoacid CoA transferase (SCOT) and α-ketoacid dehydrogenase.

17. The delivery vector of Claim 15 or Claim 16, wherein the delivery vector is a viral vector.

18. The delivery vector of Claim 17, wherein the delivery vector is an adenovirus vector.

19. A delivery vector comprising a heterologous nucleic acid that encodes an enzyme that mediates fatty acid oxidation, wherein the heterologous nucleic acid is operably linked to a control element that directs the expression of the nucleic acid in hepatic cells.

20. The delivery vector of Claim 19, wherein the enzyme that mediates fatty acid oxidation is selected from the group consisting of malonyl CoA decarboxylase, carnitinepalmitoyltransferase I, carnitinepalmitoyltransferase II, carnitine acyltranslocase, acyl-CoA

dehydrogenase, enoyl-CoA hydratase, 3-L-hydroxyacyl-CoA dehydrogenase, and β-ketoacyl-CoA thiolase.

21. The delivery vector of Claim 19 or Claim 20, wherein the delivery vector is a viral vector.

22. The delivery vector of Claim 21, wherein the delivery vector is an adenovirus vector.

23. An inhibitory oligonucleotide that is at least 8 nucleotides in length and specifically hybridizes to a target sequence encoding a ketogenic enzyme and reduces production of the ketogenic enzyme.

24. The inhibitory oligonucleotide of Claim 23, wherein the ketogenic enzyme is selected from the group consisting of β-hydroxybutyrate dehydrogenase, mitochondrial HMG-CoA synthase, acetoacetyl-CoA thiolase, and HMG-CoA lyase.

25. The inhibitory oligonucleotide of Claim 23 or Claim 24, wherein the inhibitory oligonucleotide is an antisense molecule.

26. The inhibitory oligonucleotide of Claim 23 or Claim 24, wherein the inhibitory oligonucleotide is an RNAi molecule.

27. The inhibitory oligonucleotide of Claim 26, wherein the RNAi molecule comprises a double-stranded region formed by intermolecular base pairing between two separate strands, wherein one strand comprises a sense region and the other strand comprises an antisense region.

28. The inhibitory oligonucleotide of Claim 26, wherein the RNAi molecule comprises a double-stranded region formed by intramolecular base-pairing within a single strand comprising a sense region and an antisense region.

29. The inhibitory oligonucleotide of Claim 28, wherein the RNAi molecule forms a hairpin structure.

30. The inhibitory oligonucleotide of any of Claims 26-29, wherein the RNAi comprises a double-stranded region that is 8 to 30 nucleotides in length.

31. A delivery vector comprising a heterologous nucleic acid encoding the inhibitory oligonucleotide of any of Claims 23-30, wherein the heterologous nucleic acid is operably linked to a control element that directs the expression of the nucleic acid in skeletal muscle cells.

32. A pharmaceutical formulation comprising the delivery vector of any of Claims 15-18 in a pharmaceutically acceptable carrier.

33. A pharmaceutical formulation comprising the delivery vector of any of Claims 19-22 in a pharmaceutically acceptable carrier.

34. A pharmaceutical formulation comprising the inhibitory oligonucleotide of any of Claims 23-30 or the delivery vector of Claim 31 in a pharmaceutically acceptable carrier.

35. A method of reducing ketone levels in a skeletal muscle cell comprising contacting the skeletal muscle cell with a delivery vector according to any of Claims 15-18 or 31, an inhibitory oligonucleotide according to any of Claims 23-30, or a pharmaceutical formulation according to Claim 32 or Claim 34 in an amount effective to reduce ketone levels in the skeletal muscle cell.

36. The method of Claim 35, wherein the method is carried out *in vitro*.

37. The method of Claim 35, wherein the method is carried out *in vivo*.

38. The method of Claim 37, wherein the delivery vector, inhibitory oligonucleotide or pharmaceutical formulation is administered to a subject with insulin resistance.

39. The method of Claim 37 or Claim 38, wherein the subject is obese.

40. The method of any of Claims 37-39, wherein the subject is a diabetic subject.

41. The method of any of Claims 37-40, wherein the subject is a human subject.

42. The method of any of Claims 35-41, wherein β-hydroxybutyrate levels are reduced.

43. A method of treating diabetes comprising administering a delivery vector according to any of Claims 15-18 or 31, an inhibitory oligonucleotide according to any of Claims 23-30, pharmaceutical formulation according to Claim 32 or Claim 34 to a diabetic subject in a therapeutically effective amount to reduce skeletal muscle ketone levels.

44. The method of Claim 43, wherein the delivery vector, inhibitory oligonucleotide or pharmaceutical formulation is administered to the skeletal muscle of the subject.

45. The method of Claim 43 or Claim 44, wherein skeletal muscle levels of β-hydroxybutyrate are reduced.

46. The method of any of Claims 43-45, wherein delivery vector, inhibitory oligonucleotide, or pharmaceutical formulation is administered by a route selected from the group consisting of intravenous administration, intra-arterial administration and direct administration to skeletal muscle.

47. A method of reducing ketone levels in skeletal muscle comprising administering a delivery vector according to any of Claims 19-22 or a pharmaceutical formulation according to Claim 33 to a subject in an amount effective to reduce skeletal muscle ketone levels.

48. A method of treating diabetes comprising administering a delivery vector according to any of Claims 19-22 or a pharmaceutical formulation according to Claim 33 to a diabetic subject in a therapeutically effective amount to reduce skeletal muscle ketone levels.

49. The method of Claim 47 or Claim 48, wherein the delivery vector or pharmaceutical formulation is administered to the liver of the subject.

50. The method of any of Claims 47-49, wherein skeletal muscle levels of β-hydroxybutyrate are reduced.

51. The method of any of Claims 47-50, wherein the delivery vector or the pharmaceutical formulation is administered by a route selected from the group consisting of intravenous administration, intraportal administration, intrabiliary administration, intra-arterial administration, and direct injection into the liver parenchyma.

52. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting a ketogenic enzyme with a compound; and

detecting binding of the compound to the ketogenic enzyme, wherein binding to the ketogenic enzyme identifies the compound as a candidate for the treatment of diabetes.

53. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting a ketogenic enzyme with a compound; and

detecting a reduction in ketogenic enzyme activity, wherein a reduction in ketogenic enzyme activity identifies the compound as a candidate for the treatment of diabetes.

54. A method of identifying a candidate compound for the treatment of diabetes, comprising:

contacting a cell that produces ketones with a compound;

detecting ketone levels in the cell, wherein a reduction in ketone levels identifies the compound as a candidate for the treatment of diabetes.

55. The method of Claim 54, wherein β-hydroxybutyrate levels are detected.

56. A method of identifying a candidate compound for the treatment of diabetes, comprising:

contacting a cell that produces a ketogenic enzyme with a compound;

detecting an indicia selected from the group consisting of:

(a) the concentration of the ketogenic enzyme,

(b) the ketogenic enzyme activity,

(c) the level of mRNA encoding the ketogenic enzyme, and

(d) any combination of (a) to (c),

wherein a reduction in the level of the indicia in the cell identifies the compound as candidate for the treatment of diabetes.

57. The method of any of Claims 54-56, wherein the cell is a skeletal muscle cell.

58. The method of any of Claims 54-57, wherein the cell comprises an isolated nucleic acid encoding a ketogenic enzyme.

59. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a mammalian subject,

detecting skeletal muscle ketone levels in the mammalian subject, wherein a reduction in skeletal muscle ketone levels identifies the compound as a candidate for the treatment of diabetes.

60. The method of Claim 59, wherein β-hydroxybutyrate levels are detected.

61. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a mammalian subject,

detecting an indicia in skeletal muscle selected from the group consisting of:

(a) the concentration of a ketogenic enzyme,

(b) a ketogenic enzyme activity,

(c) mRNA encoding a ketogenic enzyme, and

(d) any combination of (a) to (c),

wherein a reduction in the level of the indicia in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.

62. The method of any of Claim 59-61, wherein the mammal is an animal model of insulin resistance.

63. The method of Claim 59-61, wherein the mammal is an animal model of obesity.

64. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a transgenic non-human mammal that exhibits insulin resistance, the transgenic non-human mammal comprising an isolated nucleic acid encoding a ketogenic enzyme,

detecting the level of insulin resistance in the transgenic non-human mammal after administration of the compound, wherein a reduction in the level of insulin resistance identifies the compound as a candidate for the treatment of diabetes.

65. The method of Claim 64, wherein skeletal muscle insulin resistance is detected and a reduction in insulin resistance in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.

66. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting an enzyme that mediates fatty acid oxidation with a compound; and

detecting binding of the compound to the enzyme, wherein binding to the enzyme identifies the compound as a candidate for the treatment of diabetes.

67. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting an enzyme that mediates fatty acid oxidation with a compound; and

detecting an enhancement in enzyme activity, wherein an enhancement in enzyme activity identifies the compound as a candidate for the treatment of diabetes.

68. A method of identifying a candidate compound for the treatment of diabetes, comprising:

contacting a cell that produces an enzyme that mediates fatty acid oxidation with a compound;

detecting an indicia selected from the group consisting of:

(a) the concentration of the enzyme,

(b) the enzyme activity,

(c) the level of mRNA encoding the enzyme, and

(d) any combination of (a) to (c),

wherein an enhancement in the level of the indicia in the cell identifies the compound as candidate for the treatment of diabetes.

69. The method of Claim 68, wherein the cell is a skeletal muscle cell.

70. The method of Claim 68 or Claim 69, wherein the cell comprises an isolated nucleic acid encoding an enzyme that mediates fatty acid oxidation.

71. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a mammalian subject,

detecting an indicia in skeletal muscle selected from the group consisting of:

(a) the concentration of an enzyme that mediates fatty acid oxidation,

(b) the activity of an enzyme that mediates fatty acid oxidation,

(c) mRNA encoding an enzyme that mediates fatty acid oxidation, and

(d) any combination of (a) to (c),

wherein an enhancement in the level of the indicia in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.

72. The method of Claim 71, wherein the mammal is an animal model of insulin resistance.

73. The method of Claim 71, wherein the mammal is an animal model of obesity.

74. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a transgenic non-human mammal that exhibits insulin resistance, the transgenic non-human mammal comprising an isolated nucleic acid encoding an enzyme that mediates fatty acid oxidation,

detecting the level of insulin resistance in the transgenic non-human mammal after administration of the compound, wherein a reduction in the level of insulin resistance identifies the compound as a candidate for the treatment of diabetes.

75. The method of Claim 74, wherein skeletal muscle insulin resistance is detected and a reduction in insulin resistance in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.

76. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting a ketolytic enzyme with a compound; and

detecting binding of the compound to the ketolytic enzyme, wherein binding to the ketolytic enzyme identifies the compound as a candidate for the treatment of diabetes.

77. A method of identifying a candidate compound for the treatment of diabetes, comprising

contacting a ketolytic enzyme with a compound; and

detecting an enhancement in ketolytic enzyme activity, wherein an enhancement in ketolytic enzyme activity identifies the compound as a candidate for the treatment of diabetes.

78. A method of identifying a candidate compound for the treatment of diabetes, comprising:

contacting a cell that produces a ketolytic enzyme with a compound;

detecting an indicia selected from the group consisting of:

(a) the concentration of the ketolytic enzyme,

(b) the ketolytic enzyme activity,

(c) the level of mRNA encoding the ketolytic enzyme, and

(d) any combination of (a) to (c),

wherein an enhancement in the level of the indicia in the cell identifies the compound as candidate for the treatment of diabetes.

79. The method of any of Claim 78, wherein the cell is a skeletal muscle cell.

80. The method of Claim 78 or Claim 79, wherein the cell comprises an isolated nucleic acid encoding a ketolytic enzyme.

81. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a mammalian subject,

detecting an indicia in skeletal muscle selected from the group consisting of:

(a) the concentration of a ketolytic enzyme,

(b) the activity of a ketolytic enzyme,

(c) mRNA encoding a ketolytic enzyme, and

(d) any combination of (a) to (c),

wherein an enhancement in the level of the indicia in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.

82. The method of Claim 81, wherein the mammal is an animal model of insulin resistance.

83. The method of Claim 81, wherein the mammal is an animal model of obesity.

84. A method of identifying a candidate compound for the treatment of diabetes, comprising:

administering a compound to a transgenic non-human mammal that exhibits insulin resistance, the transgenic non-human mammal comprising an isolated nucleic acid encoding a ketolytic enzyme,

detecting the level of insulin resistance in the transgenic non-human mammal after administration of the compound, wherein a reduction in the level of insulin resistance identifies the compound as a candidate for the treatment of diabetes.

85. The method of Claim 84, wherein skeletal muscle insulin resistance is detected and a reduction in insulin resistance in skeletal muscle identifies the compound as a candidate for the treatment of diabetes.